The landscape of genomic alterations and their phenotype associations in high-risk localized prostate cancer in the Genomic Umbrella Neoadjuvant Study

Joshua M. Scurll[1], Lucia Nappi[1,2], Rainie Fu[1], Htoo Zarni Oo[1], Miles Mannas[1], Alexander Wyatt[1], Himisha Beltran[3], Peter Black[1], Neil Fleshner[4], Amina Zoubeidi[1], Martin Gleave[1]

[1]Vancouver Prostate Centre and Department of Urologic Sciences, University of British Columbia, Canada; [2]BC Cancer (Vancouver Centre), Canada; [3]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA; [4]Division of Urology, University of Toronto, Canada.

Background

High-risk localized prostate cancer (PCa) patients may benefit from neoadjuvant therapy before surgery or radiotherapy. However, rates of pathologic complete response to androgen receptor (AR) pathway inhibition are <8%. Therefore, biomarker-based selection of patients for targeted therapies might improve outcomes. An understanding of the landscape of genomic alterations, and how they relate to biological pathway activity and tumor phenotypes, in high-risk PCa is needed to inform biomarker discovery and treatment strategies. To address this need, we explored genomic and transcriptomic data from the Genomic-biomarker-selected Umbrella Neoadjuvant Study (GUNS, NCT04812366), an ongoing multi-center adaptive phase-II umbrella trial enrolling high-risk localized PCa patients for biomarker-targeted neoadjuvant combination therapies.

Methods

From September 2021 to August 2024, GUNS enrolled 97 patients at the University of British Columbia (UBC), Vancouver, and 30 at the University Health Network, Toronto. Diagnostic tumor biopsy specimens underwent Tempus' CLIA-certified 648-gene panel DNA sequencing and whole-transcriptome RNA sequencing (RNA-seq). Immunohistochemistry (IHC) was performed for PTEN. Single-sample gene set enrichment analysis (ssGSEA), unsupervised hierarchical clustering (UHC), and PAM50 classification were applied to RNA-seq data. Generalized linear modeling, followed by GSEA, was applied to GUNS and TCGA RNA-seq data to relate gene expression to several genomic alterations.

Results

Tempus successfully sequenced DNA from 105/127 patients and matching RNA from 72. *TMPRSS2-ERG* fusions (31%) were the most common genomic alteration. Excluding variants of unknown significance, the next most frequently altered genes were *FOXA1* (23%), *TP53* (14%), *SPOP* (13%), *PTEN* (12%), and *BRCA2* (9% including germline). Four patients had microsatellite instability. Two patients had functional *CDK12* mutations. Genomic differences between Asian and non-Asian patients were consistent with published data. PTEN IHC staining was negative without any reported genomic *PTEN* alteration in 12/81 UBC patients, and heterogeneous in four. UHC of RNA-seq ssGSEA data primarily separated ETS-fused tumors from *SPOP*-mutant tumors. Furthermore, PTEN loss co-occurred or clustered with ETS fusions, whereas *PTEN/AKT1* mutants clustered with *SPOP* mutants. Linear modeling and GSEA revealed distinct genotype-phenotype associations. For example, ETS fusions were associated with PCS2-luminal-subtype gene expression and decreased proliferative signatures, whereas most other major alterations were associated with PCS1-luminal-subtype gene expression. AR signatures were associated with *SPOP* and *FOXA1* mutations but not ETS fusions. *CDK12* mutations were associated with particularly aggressive gene expression signatures.

Conclusions

ETS gene fusions and *FOXA1* alterations are the most frequent alterations in the GUNS high-risk PCa cohort, albeit with differences between Asians and non-Asians consistent with published data. Transcriptomes distinguished *ETS*-fused tumors from *SPOP* mutants, and PTEN loss from *PTEN/AKT1* mutations. Inferred relationships between specific genomic alterations and gene expression signatures of luminal/basal subtypes and of biological pathways/processes, including AR signaling, proliferation,

and plasticity signatures, provide a basis to understand differences in treatment response and inform biomarker-guided treatment strategies.

Funding acknowledgements

Janssen Pharmaceuticals, Roche, Pacific Northwest Prostate Cancer SPORE, PCF Young Investigator Awards to L. Nappi and J.M. Scurll, Terry Fox Research Institute.

Conflicts of interest disclosures statement

L.N. has received research support from Janssen. M.M. has received honoraria from Janssen. A.W. has served on advisory boards and/or received honoraria from Janssen. H.B. has served as a consultant/advisory board member for Janssen. P.B. has served as a member of an advisory board or equivalent for Janssen and Roche and has been a member of a Speakers' Bureau for Janssen. N.F. has received consulting fees from Janssen. M.G. has served as a consultant for Janssen and Roche.